REMARKS

Claims 1-43 were pending. Claims 2-4, 6, 7, 9, 22, 28-30, 32 and 33 are canceled and no claims are added herein. Thus, after entry of this amendment, **claims 1, 5, 8, 10-21, 23-27, 31 and 34-43 will be pending**. Of these, claims 15-17, 24-27 and 34-43 are currently withdrawn.

Claims 1, 8, 15, 18, 21 and 24-26 are amended herein to specify that the DNA ligase polypeptide is "isolated" and to remove reference to "repair" for clarity. Claims 1, 5, 8, 15, 18, 21, 24, 26, 31, 34 and 35 are amended to recite that the DNA ligase polypeptide is at least 95% identical to accession number CAB08492 (SEQ ID NO: 91) or that the prokaryotic Ku polypeptide is at least 95% identical to accession number CAB08491 (SEQ ID NO: 92). The specification also is amended to include sequence identifiers for the recited accession numbers. Support for these amendments can be found, for example, in the claims as originally filed, and in the paragraph beginning on page 13, line 28 of the specification. Claims 1, 5, 8, 15, 18, 21, 24, 25, 26, 31, 34 and 35 are amended to comply with informalities and correct typographical errors. The amendments to withdrawn claims 15, 24, 25, 26, 34 and 35 are submitted to maintain conformance throughout the claim set.

No new matter is introduced by these amendments.

Restriction Requirement

The Office has acknowledged Applicants' election of Group I, Claims 1-14, 18-23 and 28-33, with traverse, in response to the restriction requirement set forth in the Office action dated February 25, 2009.

The restriction requirement asserted that the claims comprise eight groups, which lack a unifying special technical feature in view of Weller *et al.* (*Science* 297:1686-1689, 2002). In the response filed April 23, 2009, Applicants argued that the Weller *et al.* reference cannot serve as a basis for such a finding. Applicants submitted a Declaration under 37 CFR § 1.132 (Declaration) by Aidan J. Doherty, Marina Della, Geoffrey R. Weller, and Stephen P. Jackson, the inventors listed on the subject application. The Declaration states that any subject matter of the claimed invention that is described in Weller *et al.* is the work of the inventors alone, notwithstanding the presence of other co-authors on the reference, who worked under the direction of the inventors. Additionally, Applicants noted that Weller *et al.* was published less than one year before the filing date of the instant application and cannot serve as prior art under 35 USC § 102(b). At the

time the Declaration was filed with the Office, Marina Della was unavailable to sign the Declaration.

Applicants thank the Examiner for noting that the complete argument regarding removal of Weller *et al.* is acknowledged, but not found persuasive until perfection of Applicants' Declaration. Unfortunately, Maria Della is still unavailable to sign the Declaration. Upon submission of a perfected Declaration, Applicants understand that the requirement will be withdrawn such that Groups I through VIII will be rejoined, and all of the claims will be examined in the current case.

The current Office action further indicates that the claims of the application lack a unifying special technical feature in view of U.S. Patent No. 5,976,806 to Mahajan *et al.* (the '806 patent). As described below (in the section entitled "Rejection under 35 USC § 102") the amended claims submitted herein are novel over the '806 patent. Therefore, the amended claims comprise a special technical feature in view of this reference.

Information Disclosure Statement (IDS)

Applicants thank the Examiner for considering all the documents listed on the IDS submitted on September 27, 2006.

Objection to the Specification

The specification is objected to because Figure 12 allegedly lists sequences that appear to meet the definition for a nucleic acid sequence, but do not have associated sequence identifiers. Applicants respectfully submit that the sequences shown in Figure 12 do not require associated sequence identifiers. Figure 12 shows diagrams of the inferred NHEJ intermediates for the HO(+2) and HO(-1) events, the overhang-to-overhang events that will give a +2 reading frame (see page 15, lines 23-25 of the specification). None of these sequences are more than 10 nucleotides in length. Unless a sequence is more than 10 nucleotide in length, inclusion of a corresponding sequence identifier is not required, and is discouraged unless there is some important reason for including it (see Exhibit 1, slide 8, which is a presentation by Robert Wax at the Biotechnology, Chemical, & Pharmaceutical Customer Partnership Meeting on September 9, 2009; see also, 37 CFR 1.82(a) and MPEP 2422.03). Therefore, the sequences depicted in

Figure 12 do not need corresponding sequence identifiers. Withdrawal of the instant objection is respectfully requested.

Claim Objections

Claims 1-14, 18-23 and 28-33 are objected to as allegedly including a method that does not require the hand of man. As suggested by the Office, Applicants hereby amend the claims of the application to specify that the prokaryotic DNA ligase is an "isolated" prokaryotic DNA ligase. Withdrawal of the instant objection is respectfully requested.

Rejections under 35 USC § 112

Indefiniteness

Claims 1-14, 18-23 and 28-33 are rejected under 35 USC §112, second paragraph as allegedly being indefinite. To the extent that the rejection applies to the amended claims, Applicants traverse this rejection.

Claim 1 is rejected as indefinite for reciting "prokaryotic DNA repair ligase polypeptide" because it is allegedly not clear how a "prokaryotic DNA repair ligase polypeptide" differs from a "prokaryotic DNA ligase polypeptide." In response, claim 1 is amended to remove reference to "repair" for clarity. Claims 8, 15, 18, 21 and 24-26 are similarly amended.

Claim 5 is rejected for allegedly lacking antecedent basis for "the Mt-Lig polypeptide" and because the term "Mt-Lig polypeptide" is indefinite. Claim 5 is amended herein to remove reference to "the Mt-Lig polypeptide" rendering the rejection moot. Claim 31 is similarly amended.

Claim 8 is rejected as allegedly indefinite for the recitation of "non-compatible ends." In response, claim 8 is amended to specify that the nucleic acid ends comprises "non-complementary overhang regions."

Based on these amendments, Applicants submit claims 1, 5 and 8, and all claims dependent from these claims, are clear and definite. Accordingly, Applicants request withdrawal of these rejections under 35 USC §112, second paragraph.

Written Description

Claims 1-14, 18-23 and 28-33 are rejected under 35 USC § 112, first paragraph, as allegedly failing to comply with the written description requirement. To the extent that this rejection applies to the amended claims, Applicants traverse.

The Office asserts that claims 1-14, 18-23 and 28-33 fail the written description requirement because the specification only provides methods that employ a ligase having the amino acid sequence of accession number CAB08492. Although not in agreement with the Office's position, Applicants have amended claims 1, 8, 15, 18 and 21 to include recite "wherein the prokaryotic DNA ligase polypeptide comprises an amino acid sequence having at least 95% sequence identity to the amino acid sequence of accession number CAB08491 (SEQ ID NO: 91)" (inclusion of sequence identifier is discussed below). Because the claims are no longer directed to *any* prokaryotic DNA ligase polypeptide, Applicants believe that this rejection is moot and withdrawal of the instant rejection is respectfully requested.

Applicants note that the Office action does not specifically address the written description of claim limitations including a prokaryotic DNA ligase polypeptide comprising an amino acid sequence having at least 95% sequence identity with the amino acid sequence of accession number CAB08491 (SEQ ID NO: 91). In view of the discussion below, Applicants believe that this aspect of the amended claims complies with the written description requirement.

To satisfy the written description requirement, the specification must describe the invention in enough detail that one of skill in art concludes that the inventor was in possession of the claimed invention at the time the application was filed. *Vas-Cath Inc. v. Mahurkar*, 935 F.2d 1555, 1563 (Fed. Cir. 1991). Under this standard, description of a genus of polypeptides may be achieved by means of a recitation of a representative number of polypeptides, defined by protein sequence, falling within the scope of the genus ***or*** of a recitation of structural features common to the members of the genus (see *Regents of the University of California v. Eli Lilly and Co.*, 119 F.3d 1559 (Fed. Cir. 1997)). Under this rule, merely reciting a single member of a genus of claimed proteins will be enough to adequately describe a genus if the applicant can also supply structural information regarding the members of the genus (see also, Example 11B, Written Description Training Materials, March 25, 2008, teaching that disclosure of a single protein sequence having a claimed enzymatic activity coupled with a description of a protein domain responsible for the enzymatic activity satisfies the written description requirement).

In the instant case, the amended specification provides SEQ ID NO: 91, which is a member of the genus of prokaryotic DNA ligase polypeptides comprising an amino acid sequence having at least 95% sequence identity to the amino acid sequence of accession number CAB08492 (SEQ ID NO: 91). The specification provides information regarding the structure of SEQ ID NO: 91. For example, Figure 4 shows a domain map of CAB08491 (SEQ ID NO: 91) that highlights conserved motifs and Table 2 shows conserved motifs of prokaryotic ligases with key conserved residues within those motifs (see Table 2 and description of Table 2 on page 16 of the specification). Thus, the specification provides a member of the claimed genus, and also provides structural information regarding members of the claimed genus.

Additionally, structural information regarding ATP-dependant DNA ligases[1] was known to those of skill in the art as of the priority date of the instant application (see Exhibit 2). For example, the crystal structures of ATP-dependent DNA ligases from bacteriophage T7 (Subramanya *et al.*, *Cell*, 85:607-15, 1996; Exhibit 2A) and Chlorella virus (Odell *et al.*, *Mol. Cell.*, 6:1183-1193, 2000; Exhibit 2B) were solved and biochemical information regarding specific functional domains was available (Doherty and Wigley, *J. Mol. Biol.*, 285:63-71, 1999; Exhibit 2C). Doherty and Wigley note that "DNA ligase enzymes show striking amino acid conservation in their C-terminal region when aligned by active site…" (page 63, first paragraph of the introduction). Applicants note that what is commonly known in the art is preferably left out of the specification. *Capon v. Eshhar*, 418 F.3d 1349, 1357 (Fed. Cir. 2005). Thus, the specification provides a member of the claimed genus, and structural information regarding members of the claimed genus is described in the specification and known to those of skill in the art.

For at least the above-listed reasons, the subject matter described in the amended claims is adequately described in the specification. Accordingly, Applicants request withdrawal of this rejection under 35 USC § 112, first paragraph.

Improper Incorporation by Reference

The Office states on page 6 of the Office action that "applicant's reference to the amino acid sequence of accession number CAB08492 and CAB08491 appears to be an improper

[1] Accession number CAB08492 (SEQ ID NO: 91) refers to an ATP-dependant DNA ligase (see page 25, lines 25-32 of the specification).

incorporation by reference of essential subject matter." In response, Applicants have amended claims 1, 5, 8, 15, 18, 21, 24, 26, 31, 34 and 35 to include reference to SEQ ID NO: 91 (CAB0842) or SEQ ID NO: 92 (CAB0841) in addition to the accession numbers. The specification also is amended to include reference to these sequence identifiers and a replacement sequence listing that contains SEQ ID NO: 91 and SEQ ID NO: 92 is submitted herewith. These amendments do not introduce new matter, as discussed below.

Provided herewith is the Revision History of GenBank Accession Nos. CAB08492 (Exhibit 3A) and CAB08491 (Exhibit 3B). Included within a Revision History are GI numbers. As stated by the National Center of Biotechnology Information (NCBI; on the World Wide Web at ncbi.nlm.nih.gov), GI numbers are a series of digits that are assigned consecutively to each sequence NCBI processes. If a sequence changes in any way after its submission, it receives a new GI number, and the version number is incremented by one. The Revision Histories of GenBank Accession Nos. CAB08492 and CAB08491 clearly show that these sequences were never revised, since the GI numbers have never changed (Exhibits 3A and 3B). Since the GI numbers did not change, only revisions that did not involve the sequences were made. Therefore, the sequences for GenBank Accession No. CAB08492 and CAB08491 have not varied up to at least Applicants' filing date and in fact, as of today have always remained constant.

The Court stated in *In re Hawkins*, 486 F.2d 569, 179 USPQ 157 (CCPA 1973) that if an applicant improperly incorporates essential material by reference, "the applicant will be required to amend the disclosure to include the material incorporated by reference." *Id.* at 574.

Additionally, training material from the Patent Office provides examples of improper incorporation by reference and instructions for correcting such errors. In a presentation by Julie Burke at the Biotechnology, Chemical, & Pharmaceutical Customer Partnership Meeting on June 4, 2008, Example 3 describes a situation in which a sequence is improperly incorporated by reference. Examiners are instructed to respond to the improper incorporation by reference of essential material by requiring Applicants to comply with 37 C.F.R. § 1.57 by "providing a copy of the essential material, amending the specification to include the essential material, [and] providing a statement under 1.57(e) and (f)." (Exhibit 4, slides 31-32; Burke, "New Matter, Incorporation by Reference, Restriction, and Claim Language for Nucleic Acid Molecules").

As a first matter, Applicants clearly intended to incorporate into the application the sequences corresponding to accession numbers CAB08492 and CAB08491, as indicated by the explicit incorporation by reference statement in the specification beginning on page 13, line 30. However, because the sequences are currently considered "essential material" by the Office, the incorporation by reference of the sequences is technically improper. Applicants have corrected this in the current filing, which correction is detailed as follows:

- The claims are amended herein to refer to SEQ ID NO: 91 (the amino acid sequence of CAB08492) or SEQ ID NO: 92 (the amino acid sequence of CAB08491).
- A replacement sequence listing and statement in compliance with 37 C.F.R. § 1.821(f) are submitted herewith.
- Applicants herein provide evidence that the sequences of CAB08492 and CAB08491 never changed (Exhibit 3A and 3B, discussed above). As shown in the exhibits, each sequence has remained unchanged throughout its history as evidenced by the GI number and version number, which have remained the same in each revision. Thus, each sequence is uniquely identified, and their incorporation into the instant application does not constitute new matter.

According to MPEP § 608.01(p)(I)(A)(2), an Applicant must correct an improper incorporation by reference of essential material by "submitting an amendment to amend the specification or drawings to include the material incorporated by reference. A statement that the material being inserted is the material previously incorporated by reference and that the amendment contains no new matter is also required." The required amendment to the specification is submitted herewith. In compliance with 37 C.F.R. § 1.57(f), Applicants hereby state that the material being inserted by this amendment is the material previously incorporated by reference and that the amendment contains no new matter.

Enablement

Claims 1-14, 18-23 and 28-33 are rejected as allegedly failing to comply with the enablement requirement of 35 U.S.C. § 112, first paragraph. At page 7 of the Office action, the Office states:

> the specification, while being enabling for a method of ligating nucleic acid molecule ends comprising contacting that ligase isolated from Mycobacterium tuberculosis and having the amino acid sequence of database accession number CAB08492, does not reasonably provide enablement for any method of modifying a nucleic acid molecule comprising contacting the nucleic acid molecule with any prokaryotic DNA repair ligase polypeptide.

Specifically, the Office contends that Applicants' specification lacks sufficient guidance to predict which polypeptides may be used with the claimed method. Therefore, the specification fails to enable the claims without requiring undue experimentation on the part of the skilled artisan (see page 9, lines 18 to page 10, line 7 of the Office action). To the extent that this rejection applies to the amended claims, Applicants traverse.

The test for enablement does not hinge on predictability, but rather on whether or not the specification teaches one of skill in the art how to make and use the invention without undue experimentation. *In re Wands,* 858 F.2d 731, 737 (Fed.Cir.1988); *Genentech, Inc. v. Novo Nordisk,* 108 F.3d 1361, 1365 (Fed.Cir.1997). Lack of enablement arises where the specification requires one of ordinary skill in the art to perform "undue experimentation" to practice the invention as broadly as it is claimed. *In re Wands*, 858 F.2d at 737. The fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation. *Id.* In fact, a considerable amount of experimentation is permissible, if it is merely routine, or if the specification provides a reasonable amount of guidance in which direction the experimentation should proceed. *Id.* citing *In re Angstadt*, 537 F.2d 489, 502-504 (CCPA 1976).

The Federal Circuit identified "*Wands* factors" that may be used to determine if the amount of experimentation required to make and use an invention is unreasonable or undue. *Id.* at 737. As described in the MPEP § 2164.01(a), these factors include: a) the breadth of the claims; b) the nature of the invention; c) the state of the prior art; d) the level of ordinary skill in the art; e) the level of predictability in the art; f) the amount of direction provided by the inventor; g) the existence of working examples; and h) the quantity of experimentation needed to make or use the invention based on the content of the disclosure. Although not all the factors need to be considered, an enablement analysis cannot be limited to only one of these factors while ignoring others. MPEP §2164.01(a) citing *In re Wands*, 858 F.2d at 737.

Application of the Wands factors to the instant case supports a conclusion that the claims are enabled. For example, while the present invention is in the field of molecular biology, which is a field believed to be somewhat unpredictable, the level of skill in this field is high. *Ex Parte Kubin*, 83 U.S.P.Q.2d 1410, 1416 (B.P.A.I. 2007); *In re Wands* 858 F.2d at 740. The techniques required to practice the invention were well known to those of skill in the art. For example, the specification teaches at least a ligation of breaks assay (page 19), a terminal transfer assay (page 20), a primase assay (page 20), a nuclease assay (page 21), a plasmid repair assay (page 21) and a suicide deletion assay (page 22).

Moreover, the state of the art of protein engineering at the time of the invention was advanced. At the time of the invention, for example, *in silico* techniques were commonplace for the identification and modeling of secondary and tertiary protein structures, and variant sequences at least 95% identical to SEQ ID NO: 91 that were suitable for use in the claimed methods could be identified easily, given the teaching in the specification regarding the conserved motifs of the protein. This is not reflected in the references cited by the Examiner (*e.g.*, Ngo *et al.*), which were published years before the priority date of the application.

Further, the amended claims are limited to the use of polypeptide sequences that have at least 95% sequence identity to SEQ ID NO: 91. The Board of Patent Appeals and Interferences ("the Board") held that a claim to "...a polypeptide at least 80% identical to amino acids 22-221 of SEQ ID NO:2, wherein the polypeptide binds CD48" was enabled despite the fact that "the Specification [did] not disclose which 20%... of amino acid residues should be changed in order to maintain the biological functions for binding to CD48." *Ex parte Kubin*, 83 U.S.P.Q.2d 1410 (2007) *affirmed by In re Kubin*, 561 F.3d 1351 (Fed. Cir. 2009) (the Board's enablement finding was not appealed). In making the above findings, the Board stated:

> We agree with the examiner that molecular biology is generally an unpredictable art... However, with respect to enablement, the other *Wands* factors weigh in Appellants' favor, particularly "the state of the art" and "the relative skill of those in the art," as evidenced by the prior art teachings and Appellants' Specification. The amount of experimentation to practice the full scope of the claimed invention might have been extensive, but it would have been routine. The techniques necessary to do so were well known to those skilled in the art. *Id.* at 1416.

Similar to the instant case, the Examiner in *Kubin* had asserted that the art was unpredictable. Despite this, the Board found the claim to be enabled when all of the *Wands* factors were considered. In the instant case, the 95% sequence identity threshold, coupled with the fact that

the level of skill in the instant field is high and the general techniques required to practice the invention were well known to those of skill in the art at the time of Applicants' filing, support a finding that the amount of experimentation required to make and use the full breadth of the method of claims 1-14, 18-23 and 28-33 is not undue.

In view of the above arguments, Applicants respectfully submit that only routine experimentation is required to make and use the claimed method and that the amended claims are enabled by the specification. Accordingly, withdrawal of the instant rejection under 35 U.S.C. §112, first paragraph, is respectfully requested.

Rejection under 35 USC § 102

Claims 1, 2 and 4 are rejected under 35 USC § 102(b) as being anticipated by U.S. Patent No. 5,976,806 (the '806 patent) as evidenced by Srivastava *et al.* (*J. Biol. Chem.* 280:30273-30281, 2005). Claims 2 and 4 are canceled herein. To the extent that this rejection might apply to amended claim 1, Applicants traverse.

Amended claim 1 is limited to a method of modifying a nucleic acid molecule comprising contacting the nucleic acid molecule with an isolated prokaryotic DNA ligase polypeptide, wherein the prokaryotic DNA ligase polypeptide comprises an amino acid sequence having at least 95% sequence identity with the amino acid sequence of accession number CAB08492 (SEQ ID NO: 91). The '806 patent does not disclose the sequence of CAB08492 (SEQ ID NO: 91) or any polypeptide having at least 95% sequence identity with CAB08492 (SEQ ID NO: 91). Thus, claim 1 is not anticipated by the '806 patent. Applicants submit that this rejection is moot and request withdrawal of this rejection under 35 USC § 102(b).

CONCLUSION

Applicants believes that the foregoing comprises a full and complete response to the Office Action of record. Withdrawal of the pending rejections and allowance of the claims is respectfully requested. If the Examiner believes that there are any remaining issues in the case that could be resolved by a telephonic interview, the Examiner is encouraged to contact the representative for Applicants listed below to discuss any outstanding matters.

Respectfully submitted,

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